REMARKS

Status of the Claims

Claims 23, 28-30, 36 and 50-89 are pending.

Claims 23, 28-30, 36 and 50-89 have been rejected.

By way of this amendment, claims 23, 63 and 81 have been amended.

Upon entry into this amendment, claims 23, 28-30, 36 and 50-89 will be pending.

Summary of the Amendment

Claims 23, 63 and 81 have each been amended to more clearly refer to the claimed invention. Claims 23, 63 and 81 have each been amended to refer to "ST receptor" as "heat stable enterotoxin (ST) receptor".

Claim 23 has also been amended to expressly state that the pharmaceutical composition used in the claimed method comprises an ST receptor ligand, which is an antibody, Fab or $F(AB)_2$ "is administered in an amount effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual" and an active agent, which is an agent that causes cell death, inhibits cell division or induces differentiation, "in an amount effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual". Support for these amendments is found throughout the specification such as on page 12 lines 10-23, page 29, lines 4-11, page 29 line 21 to page 30 line 9, page 37 and pages 40-44.

Claim 63 has also been amended to expressly state that the pharmaceutical composition used in the claimed method comprises an ST receptor ligand, which is an antibody, Fab or $F(AB)_2$, and an active agent, which is an agent that causes cell death, inhibits cell division or induces differentiation. The pharmaceutical administered in the claim method is administered in an amount "effective to eliminate metastasized colorectal cancer cells". Support for these

amendments is found throughout the specification such as on page 12 lines 10-23, page 29, lines 4-11, page 29 line 21 to page 30 line 9, page 37 and pages 40-44.

Claim 81 has also been amended to expressly state that the pharmaceutical composition used in the claimed method comprises a conjugated compound. The conjugated compound comprising an ST receptor biding moiety that is an antibody, Fab or $F(AB)_2$ and an active moiety that causes cell death, inhibits cell division or induces differentiation. The conjugated compound is present "in an amount effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual". Support for these amendments is found throughout the specification such as on page 12 lines 10-23, page 29, lines 4-11, page 29 line 21 to page 30 line 9, page 37 and pages 40-44.

No new matter has been added.

Claim Objections

Claims 23, 28, 50-60, 63, 64, 68-78 and 81-84 have been objected to for not expressly referring to "ST" as "heat stable enterotoxin" in the first instance the abbreviation ST is used in the clams. Claims 23, 63 and 81 have been amended to obviate the objection. Applicant respectfully requests that the object be withdrawn.

Double Patenting Rejections

Claims 23, 28-30, 36, and 50-89 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 10, 28-31, and 54-58 of U.S. Patent No. 5,879,656.

Claims 23, 28-29, 58, 63-65, 76, 81, 82, and 85 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6 and 8 of U.S. Patent No. 6,060,037 ('037) in view of de Sauvage et al., (JBC, vol. 267, page 6479-6482, April, 1992).

As noted in previous responses, once claims have been indicated to be allowable, Applicants shall promptly provide Terminal Disclaimer as appropriate. To that end, the Examiner is invited to contact Applicants' undersigned representative and inform him of the allowability of the claims so that a Terminal Disclaimer can be promptly filed.

Rejections under 35 U.S.C. §112, second paragraph

Claims 23, 28-30, 36 and 50-89 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. It is asserted that the claims are unclear because reference to "an effective amount" is unclear. Applicants have amended each of claims 23, 63 and 81 to more clearly set forth the metes and bounds of the claims. The specification clearly and unambiguously states that therapeutically effective amount refers to an amount effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual. (page 37, lines 28-30). Thus claim 23 has been amended to indicate that each of the antibody, Fab or $F(AB)_2$ and the active agent that causes cell death, inhibits cell division or induces differentiation are present in the pharmaceutical composition in an amount effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual, while claim 81 has been amended to refer to such definition of therapeutically effective amount with reference to the amount of conjugated compound present in the pharmaceutical composition. The specification clearly and unambiguously states that the pharmaceutical compositions are used to eliminating metastatic colorectal cancer cells (page 12 lines 10-23). Thus a therapeutically effective amount useful in the treatment of metastatic colorectal cancer is an amount that will eliminate metastatic colorectal cancer cells. Claim 63 has been amended to indicate that the pharmaceutical composition comprises the antibody, Fab or $F(AB)_2$ and the active agent that causes cell death, inhibits cell division or induces differentiation are present in an amount effective to therapeutically_eliminate metastatic colorectal cancer cells.

Claims 23, 28-30, 36 and 50-89 are clear and definite and in compliance with the requirements of the second paragraph of 35 U.S.C. §112. Applicant respectfully requests that the rejection of claims 23, 28-30, 36 and 50-89 h under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

Claims 23, 28-30, 36, and 50-89 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The c1aims allegedly contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant respectfully disagrees.

The Office alleges that the specification does not teach or identify ST receptors. Okamoto is cited in support of this allegation. Applicants note that in the last paragraph of de Sauvage, F.J 1992 J. Biol. Chem. 267(10)6479-6482 (cited in obviousness type double patent rejection above), the authors explain the reason for Okamoto's incorrect analysis that questions whether ST receptors were the same as guanylyl cyclase C. The authors in de Sauvage, F.J. state that ST receptors are the same molecule as the membrane bound guanylyl cyclase on colorectal cells. Nothing in Okomato would support a finding of non-enablement.

The Office also indicates that "heat stable toxin" is a broad term which reads on many molecules. As reflected in de Sauvage, F.J., at the time of the invention one skilled in the art recognized that ST receptors were the same as the guanylyl cyclase expressed on colorectal cells and the term ST as a reference to E. cole heat stable enterotoxin was known and accepted by those skilled in the art. One skilled in the art would immediately recognize the claimed invention, which is enabled.

The Office alleges that the treatment of tumors with antibodies is unpredictable in view of Jain and Dillman. As noted in previous responses to the allegation, at the time of the invention, the technology of targeting cancer cells based on a receptor that is expressed on the cell surface was not nascent technology. At the time the application was filed, there are

numerous examples of tumor cells, specifically metastatic colon cancer cells being treated using antibodies or similar molecules. Applicant has previously submitted Takahashi *et al.* (Thoku J. Exp. Med., Vol. 168, pp. 371-374 (1992), entitled "Monoclonal Antibody-Drug Conjugate Therapy for the Patients with Colorectal Cancer"); Meredith *et al.* (*The Journal of Nuclear Medicine*, Vol. 33, pp. 1648-1653 (1992), entitled "Dose Fractionation of Radiolabled Antibodies in Patients with Metastatic Colon Cancer"), and Debinski *et al.* (*Cancer Research*, Vol. 52, pp. 5379-5385 (1992), entitled "Monovalent Immunotoxin Containing Truncated From of Psuedomonas Exotoxin as Potent Antitumor Agent") which each support the assertion that at the time of the invention, the claimed invention was enabled. At the time the application was filed, one of skill in the art had the knowledge to make and use antibodies, specifically metastatic colon cancer.

The present application and pending claims provide a new target, the ST receptor, for the antibody or other types of binding moieties that can be used to target the cancer cells. The application need not teach the general methods of administering a composition as claimed because that is something one of skill in the art could already "figure out" without undue experimentation. Some experimentation is allowed so long as it is not undue. *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404.

When the totality of evidence is viewed in its entirety, one of skill in the art would accept the objective truth of applicant's assertion that the claimed invention is enabled The evidence submitted by applicant clearly supports a finding of enablement. The evidence relied upon by the Office does not support the conclusion that the present invention is not enabled. The references cited by the Office do not contradict or cause one of skill in the art to doubt Applicant's claim that the present invention is enabled. When all of the evidence is viewed in its totality one skilled in the art would conclude that the claimed invention is enabled. The evidence of record supports a finding that the invention is enabled as required under the law.

Applicants respectfully request that the rejection of claims 23, 28-30, 36, and 50-89 under 35 U.S.C. §112, first paragraph, be withdrawn.

Conclusion

Claims 23, 28-30, 36 and 50-89 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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